AMENDMENTS TO THE SPECIFICATION

Please replace the second paragraph on page 21 with the following:

A fragment of the "monomer of an antibody" or "monomer ~~antibody"which~~ antibody" which is bound to TRAIL-R is included in the "monomer of an antibody" or "monomer antibody". The "monomer of an antibody" or "monomer antibody" can be said to be an "antibody as a single substance" or "single antibody", and "to use antibody as a monomer" can be said as "to use antibody as a single substance" or "to use antibody in the form of a single substance". An antibody which is not the "monomer of an antibody" or "monomer antibody" includes an antibody in which plural antibodies form a complex, and is said as a "polymer (multimer) of antibodies" or "polymer (multimer) antibody". The complex formed by plural antibodies can be formed by the cross-linker mentioned above or by the polymerization of two or more of antibody molecules. When the "monomer of an antibody" or "monomer antibody" is used, it can consist of a mixture with the "polymer (multimer) of antibodies" or "antibody polymer (multimer)". In this case, the mixture contains the "polymer (multimer) of antibodies" or "antibody polymer (multimer)" by 0.5% or less, preferably 0.2% or less, more preferably 0.1% or less. Most preferably, the "polymer (multimer) of antibodies" or "antibody polymer (multimer)" is not contained.

Please replace the first full paragraph on page 22 with the following paragraph:

That is to say, the "monomer of an antibody" or "monomer antibody" of the present ~~inventionis~~ invention is an antibody which has the activity to induce apoptosis in a cell without depending on (independently of) the "exogenous factor" or "factor present exogenously".

Please replace the last paragraph on page 69, ending on page 27, with the following:

Fig. 5a to l and Table 5 show the results. In Fig. 5, a solid line with solid circles (-●-) expresses normal human hepatocyte, and a dotted line with solid diamond-shaped symbols (-- ◆--) expresses Colo205 cells. Furthermore, Fig. 5k and l show the results of experiments wherein no goat anti-human IgG(γ)-specific polyclonal antibodies were added. Table 5 shows the cell-death-inducing activity (LD50 value) of the purified human anti-TRAIL-R2

monoclonal antibody on colon carcinoma cells Colo205, and normal human hepatocytes. 2.5×10^3 colon carcinoma cells Colo205, were seeded in 100 μl of a medium per well of a 96-well flat-bottomed plate, and the purified human anti-TRAIL-R2 monoclonal antibodies were added to the cells on the next day. When the time for the reaction between the cells and the antibody reached ~~48hours~~ 48 hours, the LD50 value was obtained. 7.5×10^4 normal cells (human hepatocytes) were seeded in 100 μl of a medium per well of a 96-well flat-bottomed plate, and the purified human anti-TRAIL-R2 monoclonal antibodies were added to normal cells (human hepatocytes) on the next day. When the time for the reaction between the cells and antibody reached to 24 hours, the LD50 value was obtained. Compared with the negative control, the purified human anti-TRAIL-R2 monoclonal antibody was shown to clearly have activity to induce cell death in Colo205 cells. Furthermore, compared with the human recombinant TRAIL and purified antibody H-48-2, the human hepatocyte toxicity of the purified human anti-TRAIL-R2 monoclonal antibodies E-11-13, L-30-10 and KMTR1 were shown to be low.

Please replace the third paragraph on page 85 with the following:

The translation initiation point of the heavy chain DNA is an ATG codon that begins from the 30th adenine (A) from the 5' end of SEQ ID NO: 16. The boundary of the antibody variable region and the constant region is located between the 461st adenine (A) and the 462nd guanine (G) from the ~~5'end~~ 5' end. In the amino acid sequence, the heavy chain variable region ranges from the N-terminus to the 144th serine (S) residue of SEQ ID NO: 17, and the constant region is of the 145th alanine (A) and the following residues. Analysis of the N-terminus of the purified heavy chain protein revealed that the heavy chain signal sequence ranges from the N-terminus to the 26th serine (S) of SEQ ID NO: 17, and the N-terminus of the mature protein is the 27th glutamine (Q) of SEQ ID NO: 17.

Please replace the first paragraph on page 101 with the following:

By the activity to induce cell death on carcinoma cells described in Example 7, ELISA described in Examples 4 and 5 and the FACS analysis described in Example 6, a large number of hybridomas producing human monoclonal antibodies that have the activity to induce cell death only by the hybridoma culture supernatant, and have human

immunoglobulin γ chain (hIg γ) and human immunoglobulin light chain κ, and have reactivity specifically to human TRAIL-R2 were obtained. Furthermore, in any of the following examples including this example, and tables and figures showing the test results of the examples, hybridoma clones producing each of the human anti-human TRAIL-R2 monoclonal antibodies of the present invention were denoted using symbols. A clone represented by symbols with the term "antibody" placed before or after the symbols means an antibody that is produced by each of the hybridomas, or a recombinant antibody that is produced by a host cell carrying an antibody gene (full-length or a variable region) isolated from the hybridoma. In addition, within a contextually clear range, the name of a hybridoma clone may express the name of an antibody. The following hybridoma clones represent single ~~clones:0304~~ clones: 0304 and 0322. 0304 was internationally deposited as described above.

Please replace the last two paragraphs on page 118, ending on page 119 with the following:

As Fig. 18b shows, the monomer fraction of H-48-2 antibody which is monomer inactive antibody had no cell-death-inducing activity when used alone but had the activity when used in the presence of hPBMC as a cross-linker. The activity in the presence of hPBMC as a cross-linker was neutralized by excess amount of the competition antibody. This suggests that the activity of H-48-2 is affected by an endogenous cross-linker. Furthermore, since the neutralization by the competition antibody was caused by masking Fc receptor (hereinafter, referred to as FcR) on effecter cells in hPBMC, it is thought that FcR is involved in the cross-linking. On the contrary, 0304 which is the antibody of which monomer fraction has the activity (hereinafter ~~reffered~~ referred to as monomer active antibody) has the activity as a monomer fraction alone independently of hPBMC. Furthermore, since the activity in the presence of hPBMC was not neutralized at all by excessive amount of the competition antibody, the activity of 0304 was revealed not to be affected by an endogenous cross-linker. Consequently, it was shown that the activity ~~ofmonomer~~ of monomer active antibody, unlike monomer inactive antibody, is not affected by hPBMC which is thought to be an endogenous cross-linker as well as goat anti-human IgG (γ)-specific polyclonal antibody which is thought to be an artificial cross-linker, and the activity is expected independently of a cross-linker.

Please replace the last paragraph on page 119, ending on page 120 with the following:

Regarding the cell-death-inducing activity of the monomer fraction of the human anti-TRAIL-R2 antibody, 0304-IgG1 and H-48-2, which were obtained by the method described in Example 27, the requirement of hPBMC (including Fc receptor positive cells) which is thought to be an endogenous cross-linker and the contribution of cross-linking by FcR were examined. Colo205 cells which had been cultured in RPMI-1640 medium containing 10% FCS were collected by Trypsin-EDTA treatment and prepared at the concentration of $5x10^4$/ml. The cells were added to each well of 96-well flat-bottomed plate (Beckton Dickinson) at 100 μl/well. After 24 hours of culturing at 37°C under 5.0% carbon dioxide gas, a monomer fraction of the human anti-TRAIL-R2 monoclonal antibody and the unfractionated anti-DNP human IgG1 antibody as a negative control were added at the final concentration of 1μg/ml to each well (10 μl/well). After 0.5-1 hours of culturing at 37°C under 5.0% carbon dioxide gas, the suspension of human PBMC was added at 10 μl/well to adjust E/T ratio (E: effector cell, T: target cell, E and T show respectively, human PBMC and a carcinoma cell in this example) the value indicated in figures. As a comparative control, the wells to which the antibody was added alone and wells added with goat anti-human IgG (γ)-specific polyclonal antibody as a cross-linker were prepared. Furthermore, to investigate whether or not the cross-linking by human PBMC is involved by Fc receptor, some hPBMCs was treated with anti-CD16 antibody (Pharmingen)/ anti-CD32 antibody (Selotec)/ anti-CD64 antibody (Caltag Laboratories) mixture (hereinafter, ~~reffered~~ referred to as FcR blocker) at each concentration of 10 μg/ml per $1x10^7$ cells for more than 30 minutes. Then, the cell suspension was added without being washed. Alternatively, excessive amount (100 times the amount of anti-TRAIL-R2 antibody) of a competition antibody (control IgG1: anti-HSA human antibody) was added for the same purpose. After the addition of the human PBMC, the plate was gently shaken such that the carcinoma cells were not detached, and cultured at 37°C under 5.0% carbon dioxide gas. After culturing for 2 days, each well was washed mildly with PBS and added with fresh RPMI-1640 medium containing 10% FCS. Consequently, 20 μl of MTS reagent (Cell Titer 96® AQUEOUS Non-Radioactive Cell Proliferation Assay: Promega) was added to each well. After additional 2-3 hours of culturing at 37°C under 5.0% carbon dioxide gas, absorbance at a wavelength of 490 nm (reference wavelength of 630 nm) was measured using a microplate reader (SPECTRA MAX 250: Molecular Devices). Using the reducibility of mitochondria as an indicator, the survival rate of the cells was calculated using the formula of Example 29.

Please replace the last paragraph on page 120 with the following:

As shown in Figures 19a, the monomer fraction of H-48-2 which was monomer inactive antibody did not have the cell-death-inducing activity alone also in this study. It had the cell-death-inducing activity when goat anti-human IgG (γ)-specific polyclonal antibody or hPBMC was co-existed as a cross-linker. This shows that the activity of H-48-2 is affected by a cross-linker. Furthermore, since the activity in the presence of hPBMC as a cross-linker was neutralized in the presence of excessive amount of the competition antibody, it was shown that FcR is involved in cross-linking. On the contrary, 0304-IgG1 which was monomer active ~~antibodyhad~~ antibody had the activity when used as an antibody alone independently of hPBMC and the activity was not neutralized at all even in the presence of super excessive competition antibody. From the results, it is confirmed that the activity of 0304 is not affected by a cross-linker.

Please replace the second paragraph on page 121 with the following:

The same findings were also observed in the results shown in Figure 19b. That is, the monomer fraction of H-48-2 which is monomer inactive antibody had no cell-death-inducing activity used as a single substance at a concentration of 1μg/ml, but had the activity when used in the presence of hPBMC as a cross-linker. This shows that the activity of H-48-2 is affected by a cross-linker. Furthermore, the activity when hPBMC was co-existed as a cross-linker was neutralized by previously treating hPBMC with FcR blocker. This shows that FcR is involved in cross-linking. On the contrary, 0304-IgG1 had the activity when used ~~aloneindependently~~ alone independently of hPBMC and the activity was not neutralized at all by the pretreatment of hPBMC with FcR blocker. This clearly supports the findings that the activity of 0304 does not depend on a cross-linker.

Please replace the first paragraph of Example 31 on page 122 with the following:

Example 31 The activity of a monomer active antibody for inducing aggregation of TRAIL-R2 molecules on the surface of cells to investigate the affect of the treatment of an antibody on behavior of a receptor molecule which exists on the surface of cells, 0304 which is a monomer active antibody. H-48-2 which is a monomer inactive antibody and a chemical cross-linker (DTSSP, Pierce) were used to perform the following studies. $6x10^6$

cells of Colo205 cells, which were human colon carcinoma cells, were suspended in 0.3ml of PBS, 7.2 μg of each antibody in the monomer fraction of human anti-TRAIL-R2 antibodies, 0304-IgG1 and H-48-2, obtained by the method described in Example 27 was added to the suspension and the cells were incubated at 37°C for ~~10minutes~~ 10 minutes. Then, the cell suspension was centrifuged to remove the supernatant containing unbound antibodies and the suspension was re-suspended in 0.5ml of PBS to wash and remove the unbound antibodies. The thus obtained cell suspension was suspended in 0.3ml of PBS and a chemical cross-linker solution (200mM DTSSP) was added to the suspension at a final concentration of 2mM. After standing the suspension on ice for 2 hours, 1M Tris-HCl pH7.5 was added at a final concentration of 50mM to inactivate the excessive chemical cross-linker and the suspension was stood on ice for 15 minutes. Then, the cells were collected by centrifugation, the supernatant was removed, the cell lysing solution (PBS containing 0.1% Triton X-100), 9 times the volume of cell pellet, was added, cells were completely suspended and the suspension was stood on ice for 30 minutes. After the increase of transparency of the cell suspension was observed, the suspension was centrifuged for 30 minutes to remove insoluble fraction. The obtained soluble fraction was referred to as cell lysate solution. 100μl of the lysate solution was subjected to gel filtration analysis and the distribution of the molecular weight of antibody-antigen complex which were cross-linked was investigated.